

Applicant: Evans and Blumberg
Application No.: 09/458,366
Filed: December 9, 1999
Page 2

PATENT
Attorney Docket No. SALK2270-2

-- 13. (New) A transgenic mouse whose genome contains a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to an inducible promoter/enhancer,

wherein said SXR polypeptide is a member of the steroid/thyroid hormone superfamily and forms a heterodimer with retinoid X receptor,

wherein said SXR polypeptide binds to a direct or inverted repeat response element based on the half site RGBNNM,

wherein:

R is selected from A or G;

B is selected from G, C, or T;

each N is independently selected from A, T, C, or G; and

M is selected from A or C;

with the proviso that at least 4 nucleotides of said -RGBNNM- sequence are identical with the nucleotides at corresponding positions of the sequence AGTTCA;

wherein said SXR polypeptide inducibly activates transcription in response to a wide variety of natural and synthetic steroid hormones, including at least compounds that induce catabolic enzymes, steroid receptor agonists and antagonists, and bioactive dietary compounds, and

wherein said transgenic mouse expresses said SXR polypeptide in at least one of the liver and intestine.

14. (New) A transgenic mouse according to claim 13, wherein expression of said SXR polypeptide in at least one of the liver and intestine activates in the transgenic mouse a response to natural and synthetic steroid hormones to which a wild type mouse does not respond.

Applicant: Evans and Blumberg
Application No.: 09/458,366
Filed: December 9, 1999
Page 3

PATENT
Attorney Docket No. SALK2270-2

15. (New) A transgenic mouse according to claim 13, wherein said SXR polypeptide comprises an SXR ligand binding domain and a DNA binding domain obtained from a transcription activating factor.

16. (New) A transgenic mouse according to claim 13, wherein the ligand binding domain and DNA binding domain of said SXR polypeptide are obtained from SXR.

17. (New) A transgenic mouse according to claim 13, wherein said mouse is further transformed with a vector which comprises:

- (a) a promoter that is operable in said mouse,
- (b) a hormone response element, and
- (c) DNA encoding a protein,

wherein said protein-encoding DNA is operatively linked to said promoter for transcription of said DNA, and

wherein said promoter is operatively linked to said hormone response element for activation thereof.

18. (New) A transgenic mouse according to claim 17, wherein said protein is a reporter.

19. (New) A transgenic mouse according to claim 17, wherein said protein is a mammalian cytochrome p450.

20. (New) A transgenic mouse according to claim 13, wherein the promoter/enhancer is the albumin promoter/enhancer.

21. (New) A transgenic mouse according to claim 13, wherein the transgene further comprises nucleic acid sequence encoding VP16.

Applicant: Evans and Blumberg
Application No.: 09/458,366
Filed: December 9, 1999
Page 4

PATENT
Attorney Docket No. SALK2270-2

22. (New) Cells derived from a transgenic mouse according to claim 13.

23. (New) A transgenic knock-out mouse whose genome comprises a homozygous disruption in an endogenous SXR polypeptide gene, wherein said homozygous disruption prevents function of an endogenous SXR polypeptide and results in said transgenic knockout mouse exhibiting decreased response to steroids and xenobiotics as compared to a wild-type mouse.

24. (New) A transgenic mouse whose genome contains a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to a constitutively active promoter/enhancer,

wherein said SXR polypeptide is a member of the steroid/thyroid hormone superfamily and forms a heterodimer with retinoid X receptor,

wherein said SXR polypeptide binds to a direct or inverted repeat response element based on the half site RGBNNM,

wherein:

R is selected from A or G;

B is selected from G, C, or T;

each N is independently selected from A, T, C, or G; and

M is selected from A or C;

with the proviso that at least 4 nucleotides of said -RGBNNM- sequence are identical with the nucleotides at corresponding positions of the sequence AGTTCA;

Applicant: Evans and Blumberg
Application No.: 09/458,366
Filed: December 9, 1999
Page 5

PATENT
Attorney Docket No. SALK2270-2

wherein SXR polypeptide inducibly activates transcription in response to a wide variety of natural and synthetic steroid hormones, including at least compounds that induce catabolic enzymes, steroid receptor agonists and antagonists, and bioactive dietary compounds, and

wherein said transgenic mouse expresses said SXR polypeptide in at least one of the liver and intestine.

25. (New) A transgenic mouse according to claim 24, wherein constitutive expression of said SXR polypeptide results in growth retardation and hepatomegaly in said mouse.

26. (New) A transgenic mouse according to claim 24, wherein said SXR polypeptide comprises an SXR ligand binding domain and a DNA binding domain obtained from a transcription activating factor.

27. (New) A transgenic mouse according to claim 24, wherein the ligand binding domain and DNA binding domain of said SXR polypeptide are obtained from SXR.

28. (New) A transgenic mouse according to claim 24, wherein said mouse is further transformed with a vector which comprises:

- (a) a promoter that is operable in said mouse,
- (b) a hormone response element, and
- (c) DNA encoding a protein,

wherein said protein-encoding DNA is operatively linked to said promoter for transcription of said DNA, and

wherein said promoter is operatively linked to said hormone response element for activation thereof.

Applicant: Evans and Blumberg
Application No.: 09/458,366
Filed: December 9, 1999
Page 6

PATENT
Attorney Docket No. SALK2270-2

29. (New) A transgenic mouse according to claim 28, wherein said protein is a reporter.
30. (New) A transgenic mouse according to claim 28, wherein said protein is a mammalian cytochrome p450.
31. (New) A transgenic mouse according to claim 28, wherein the response element in the reporter vector is based on the half site RGBNNM,
- wherein:
- R is selected from A or G;
 - B is selected from G, C, or T;
 - each N is independently selected from A, T, C, or G; and
 - M is selected from A or C;
- with the proviso that at least 4 nucleotides of said -RGBNNM- sequence are identical with the nucleotides at corresponding positions of the sequence AGTTCA.
32. (New) A transgenic mouse according to claim 24, wherein the promoter/enhancer is the VP16 promoter/enhancer.
33. (New) A transgenic mouse according to claim 24, wherein the transgene further comprises nucleic acid sequence encoding VP16.
34. (New) Cells derived from a transgenic mouse according to claim 24.

Applicant: Evans and Blumberg
Application No.: 09/458,366
Filed: December 9, 1999
Page 7

PATENT
Attorney Docket No. SALK2270-2

35. (New) A method for producing a transgenic mouse, said method comprising:

injecting a one-cell mouse zygote with a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to an inducible or a constitutively active promoter/enhancer,

wherein said SXR polypeptide is a member of the steroid/thyroid hormone superfamily and forms a heterodimer with retinoid X receptor,

wherein said SXR polypeptide binds to a direct or inverted repeat response element based on the half site RGBNNM,

wherein:

R is selected from A or G;

B is selected from G, C, or T;

each N is independently selected from A, T, C, or G; and

M is selected from A or C;

with the proviso that at least 4 nucleotides of said -RGBNNM- sequence are identical with the nucleotides at corresponding positions of the sequence AGTTCA, and inducibly or constitutively activates transcription in response to a wide variety of natural and synthetic steroid hormones, including at least compounds that induce catabolic enzymes, steroid receptor agonists and antagonists, and bioactive dietary compounds, and

wherein said polypeptide is detectably expressed in at least one of the liver and the intestine, and ,

obtaining from the zygote a transgenic mouse that expresses said SXR polypeptide in the liver.